

## PATENT COOPERATION TREATY

not file

284270

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

CHIRON CORPORATION  
Intellectual Property Department  
Attn. Alexander, Lisa E.  
P.O. Box 8097  
Emeryville, CA 94662-8097  
UNITED STATES OF AMERICA

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL SEARCH REPORT AND  
THE WRITTEN OPINION OF THE INTERNATIONAL  
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

Applicant's or agent's file reference

PP22244.002

International application No.

PCT/US2004/037159

Applicant

CHIRON CORPORATION

Date of mailing  
(day/month/year)

17/06/2005

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International filing date  
(day/month/year)

04/11/2004

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

**Filing of amendments and statement under Article 19:**

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

**When?** The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

**Where?** Directly to the International Bureau of WIPO, 34 chemin des Colombettes  
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.
3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.
- ☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

**4. Reminders**

Shortly after the expiration of 18 months from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the PCT Applicant's Guide, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority



European Patent Office, P.B. 5818 Patentlaan 2  
NL-2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Michele Digiusto

DOCKETED only SZL17-05

Atty LEA PA

File # PP022244.0002

Due Date Ext

Final Date 8-17-05 DLF dt-19

9-17-05 RSD W. 9

## NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

### INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only.

#### What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

#### When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

#### Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

#### How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

#### What documents must/may accompany the amendments?

##### Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

## NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped), whether

- (i) the claim is unchanged;
- (ii) the claim is cancelled;
- (iii) the claim is new;
- (iv) the claim replaces one or more claims as filed;
- (v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:  
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."
2. [Where originally there were 15 claims and after amendment of all claims there are 11]:  
"Claims 1 to 15 replaced by amended claims 1 to 11."
3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:  
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or  
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."
4. [Where various kinds of amendments are made]:  
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

### "Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

### Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

### Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

# PATENT COOPERATION TREATY

# PCT

## INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference <b>PP22244.002</b>	<b>FOR FURTHER ACTION</b> <small>see Form PCT/ISA/220 as well as, where applicable, Item 5 below.</small>	
International application No. <b>PCT/US2004/037159</b>	International filing date (day/month/year) <b>04/11/2004</b>	(Earliest) Priority Date (day/month/year) <b>04/11/2003</b>
Applicant  <b>CHIRON CORPORATION</b>		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

**1. Basis of the report**

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ The international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. ☒ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ Certain claims were found unsearchable (See Box II).

3. ☐ Unity of invention is lacking (see Box III).

4. With regard to the title,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the drawings,

a. the figure of the drawings to be published with the abstract is Figure No. \_\_\_\_\_

☐ as suggested by the applicant.

☐ as selected by this Authority, because the applicant failed to suggest a figure.

☐ as selected by this Authority, because this figure better characterizes the invention.

b. ☒ none of the figures is to be published with the abstract.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US2004/037159

## Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:
  - a. type of material
    - ☒ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material
    - ☒ in written format
    - ☒ in computer readable form
  - c. time of filing/furnishing
    - ☒ contained in the international application as filed
    - ☒ filed together with the international application in computer readable form
    - ☐ furnished subsequently to this Authority for the purpose of search
2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
3. Additional comments:

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US2004/037159

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 A61P35/02 A61K39/395  
//C07K16/28

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS, Sequence Search, PAJ

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 02/28480 A (CHIRON CORPORATION; CHU, KETING; MASUOKA, LORIANNE) 11 April 2002 (2002-04-11)  page 30	1-9, 19-24, 29-42, 46-61
A	WO 02/28940 A (NIPPON KAYAKU KABUSHIKI KAISHA; AKATSUKA, YASUMASA; ASANO, TOYOFUMI; I) 11 April 2002 (2002-04-11) figure 12	1-64
A	WO 01/83755 A (GEMINI SCIENCE, INC; MIKAYAMA, TOSHIFUMI; TAKAHASHI, NOBUAKI; CHEN, XI) 8 November 2001 (2001-11-08) page 9  -/--	1-64

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

\* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*8\* document member of the same patent family

Date of the actual completion of the international search

11 May 2005

Date of mailing of the international search report

17/06/2005

Name and mailing address of the ISA  
European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Wagner, R

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/US2004/037159

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02/088186 A (KIRIN BEER KABUSHIKI KAISHA; MIKAYAMA, TOSHIFUMI; YOSHIDA, HITOSHI; FO) 7 November 2002 (2002-11-07) example 14	1-64
P,A	-& EP 1 391 464 A (KIRIN BEER KABUSHIKI KAISHA) 25 February 2004 (2004-02-25)	1-64
A	WO 03/029296 A (CHIRON CORPORATION; CHU, KETING; WANG, CHANGYU; YOSHIHARA, CORRINE; DO) 10 April 2003 (2003-04-10) example 13	1-64
A	FUNAKOSHI S ET AL: "DIFFERENTIAL IN VITRO AND IN VIVO ANTITUMOR EFFECTS MEDIATED BY ANTI-CD40 AND ANTI-CD20 MONOCLONAL ANTIBODIES AGAINST HUMAN B-CELL LYMPHOMAS" JOURNAL OF IMMUNOTHERAPY: WITH EMPHASIS ON TUMOR IMMUNOLOGY, RAVEN PRESS, US, vol. 19, no. 2, March 1996 (1996-03), pages 93-101, XP001064650 ISSN: 1067-5583 the whole document	1-64
A	WO 02/04021 A (IDEC PHARMACEUTICALS CORPORATION) 17 January 2002 (2002-01-17) the whole document	1-64
A	WO 02/22212 A (IDEC PHARMACEUTICALS CORPORATION) 21 March 2002 (2002-03-21) the whole document	1-64
A	MALONEY D G ET AL: "IDEC-C2B8: RESULTS OF A PHASE I MULTIPLE-DOSE TRIAL IN PATIENTS WITH RELAPSED NON-HODGKIN'S LYMPHOMA" JOURNAL OF CLINICAL ONCOLOGY, GRUNE AND STRATTON, NEW YORK, NY, US, vol. 15, no. 10, October 1997 (1997-10), pages 3266-3274, XP002936242 ISSN: 0732-183X the whole document	1-64

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US2004/037159

## Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claims 1-64 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/037159

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0228480	A	11-04-2002	AU 1136602 A	15-04-2002
			AU 9650701 A	15-04-2002
			AU 9654501 A	15-04-2002
			AU 9654701 A	15-04-2002
			CA 2424296 A1	11-04-2002
			CA 2424749 A1	11-04-2002
			EP 1322383 A2	02-07-2003
			EP 1326896 A2	16-07-2003
			JP 2004510752 T	08-04-2004
			JP 2004517611 T	17-06-2004
			WO 0228904 A2	11-04-2002
			WO 0228905 A2	11-04-2002
			WO 0228480 A2	11-04-2002
			WO 0228481 A2	11-04-2002
WO 0228940	A	11-04-2002	EP 1323761 A1	02-07-2003
			WO 0228940 A1	11-04-2002
			JP 2002241475 A	28-08-2002
			US 2003009001 A1	09-01-2003
			US 2004166326 A1	26-08-2004
WO 0183755	A	08-11-2001	AU 5921501 A	12-11-2001
			WO 0183755 A2	08-11-2001
			US 2003059427 A1	27-03-2003
			US 2002142358 A1	03-10-2002
WO 02088186	A	07-11-2002	US 2003059427 A1	27-03-2003
			CA 2445349 A1	07-11-2002
			CN 1522264 A	18-08-2004
			EP 1391464 A1	25-02-2004
			WO 02088186 A1	07-11-2002
			US 2004120948 A1	24-06-2004
			AU 5921501 A	12-11-2001
EP 1391464	A	25-02-2004	US 2003059427 A1	27-03-2003
			US 2002142358 A1	03-10-2002
			CA 2445349 A1	07-11-2002
			EP 1391464 A1	25-02-2004
			US 2004120948 A1	24-06-2004
			CN 1522264 A	18-08-2004
			WO 02088186 A1	07-11-2002
			AU 5921501 A	12-11-2001
WO 03029296	A	10-04-2003	WO 03029296 A1	10-04-2003
WO 0204021	A	17-01-2002	US 2002006404 A1	17-01-2002
			AU 6461201 A	21-01-2002
			CA 2415100 A1	17-01-2002
			CN 1446104 A	01-10-2003
			EP 1305045 A1	02-05-2003
			JP 2004502742 T	29-01-2004
			MX PA03000306 A	05-04-2004
			NO 20030128 A	12-03-2003
			WO 0204021 A1	17-01-2002
			US 2002028178 A1	07-03-2002
			ZA 200300293 A	22-01-2004
			CA 2436180 A1	08-08-2002
			CA 2444661 A1	08-08-2002

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US2004/037159

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0204021 A		CN 1494433 A	05-05-2004
		EP 1370292 A1	17-12-2003
		EP 1372724 A2	02-01-2004
		JP 2005503999 T	10-02-2005
		JP 2005503326 T	03-02-2005
		NO 20033417 A	30-09-2003
		NO 20033418 A	30-09-2003
		WO 02060484 A1	08-08-2002
		WO 02060485 A2	08-08-2002
		US 2002159996 A1	31-10-2002
WO 0222212 A	21-03-2002	CA 2422076 A1	21-03-2002
		JP 2004508420 T	18-03-2004
		MX PA03002262 A	15-10-2003
		NO 20031218 A	19-05-2003
		WO 0222212 A2	21-03-2002
		US 2002058029 A1	16-05-2002
		ZA 200302139 A	23-06-2004
		AU 9103701 A	26-03-2002
		EP 1328320 A2	23-07-2003

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

## PCT

To:

see form PCT/ISA/220

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**  
(PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference see form PCT/ISA/220		<b>FOR FURTHER ACTION</b> See paragraph 2 below	
International application No. PCT/US2004/037159	International filing date (day/month/year) 04.11.2004	Priority date (day/month/year) 04.11.2003	
International Patent Classification (IPC) or both national classification and IPC A61P35/02, A61K39/395			
Applicant CHIRON CORPORATION			

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.



If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

9-17-05

9-4-05

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

<p>Name and mailing address of the ISA:</p> <div style="text-align: center;">  </div> <p>European Patent Office D-80293 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465</p>	<p>Authorized Officer</p> <p style="text-align: center;">Wagner, R</p> <p>Telephone No. +49 89 2399-7357</p> <div style="text-align: right;">  </div>
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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

**10/578401**

International application No.  
PCT/US2004/037159

**IP20Rec'd PCT/PTO 03 MAY 2006**

**Box No. I Basis of the opinion**

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☒ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☒ in written format
    - ☒ in computer readable form
  - c. time of filing/furnishing:
    - ☒ contained in the international application as filed.
    - ☒ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2004/037159

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**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

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The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-64 (IA)

because:

☒ the said international application, or the said claims Nos. 1-64 regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/US2004/037159

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or  
industrial applicability; citations and explanations supporting such statement**

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**1. Statement**

Novelty (N)	Yes: Claims	1-64
	No: Claims	
Inventive step (IS)	Yes: Claims	10-18,25-28,43-45,62-64
	No: Claims	1-9,19-24,29-42,46-61
Industrial applicability (IA)	Yes: Claims	-
	No: Claims	

**2. Citations and explanations**

**see separate sheet**

**WRITTEN OPINION OF THE  
 INTERNATIONAL SEARCHING  
 AUTHORITY (SEPARATE SHEET)**

PCT/US2004/037159

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 1-64 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item V**

**Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Reference is made to the following documents:  
 D1: WO02/28480  
 D2: WO02/28940  
 D3: WO01/83755  
 D4: WO02/88186 (EP1391464)  
 D5: WO03/029296
  
2. For the assessment of the present claims 1-64 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.
  
3. All claims are directed to methods of combination treatment of cancer characterised by neoplastic B cell growth by the combination of an anti-CD20 antibody and an anti-CD40 antibodies, which does not have an agonist activity. All claims are further limited by two human antibodies CHIR-5.9 and CHIR-12.12, the light or heavy chains of said antibodies, antibodies which bind the same epitopes as CHIR-5.9 and CHIR-

12.12 or which compete with the binding of the said two antibodies. As the antibodies CHIR-5.9 and CHIR-12.12 are new and as the prior art does not disclose antibodies with the same antagonist effect, which bind the same epitope or domain of CD40 as CHIR-5.9 or CHIR-12.12 the methods using said antibodies (claims 1-64) are also considered to be new (Article 33(2) PCT).

D1 discloses (page on page 30, line 20) that anti-CD40 antibodies with antagonist properties can be used in combination with the anti-CD20 antibody (Rituxan®) for the treatment of cancer involving malignant B cells. The preferred anti-CD40 antibody disclosed in D1 is called 15B8, and is fully disclosed by its sequence (figure 12) in the co-pending application PCT/us01/30857, published as WO 02/28904(D2), which shares the priority of D1. Antibody 15B8 does not bind to the same epitope as the antibodies CHIR-5.9 and CHIR-12.12, but is only one example of known human antibodies against CD40, which do not have an agonist activity. Other human antibodies against CD40 are disclosed in

D3 discloses human anti-CD40 antibodies, which are antagonists (page 9, lines 20-25). D3 discloses also the use of the anti-CD40 antibodies in the treatment of cancer (page 30, lines 1-7)

D4 discloses also several human anti-CD40 antibodies, which have an antagonist effect (example 14).

The difference between the disclosure D1 and of the present independent claims lies in the use of different human anti-CD40 antibodies as a partner in the combination therapy with Rituxan® in the treatment of B cell tumours. The technical problem to be solved can be formulated as the provision of alternative anti-CD40 antibodies without significant agonist activities. As the prior art D2, D3 and D1 disclose already human antibodies having said properties and as the methods for producing human antibodies are well-known in the art, the provision of alternative antibodies cannot be regarded as involving an inventive step (Article 33(3) PCT). Therefore the subject-matter of independent claims 1, 19, 29, 48 does not involve an inventive step (Article 33(3) PCT). The additional features of independent claims 2-9, 20-24, 30-42 and 49-61 do not induce any surprising effect and therefore do not confer an inventive step



on the method (Article 33(3) PCT). It must be noted that the dependent claims 2, 0, 30, 49 are only supported by the description as far as the B-cell tumour to be treated is refractory to treatment with the CD-20 antibody (see section 4 below). As no synergistic effect was shown for any other B-cell tumour an inventive step cannot be acknowledged for the entire width of the scope claimed in claims 2, 20, 30, 49.

4. Claims 10-18, 25-28, 43-45 and 62-64 are directed to the treatment of tumours comprising neoplastic B cells by the combination treatment comprising a non-agonist anti-CD40 antibody and an anti-CD20 antibody. Although D1 has proposed the combined use of said antibodies in the treatment of B cell tumours, D1 does not propose the combined use in anti-CD20 refractory patients. D5 (example 13) proposes the use of antagonist anti-CD40 antibodies for the treatment of anti-CD20 refractory patients. The prior art does not give any indication that the tumour growth of B-cells refractory to anti-CD20 could be inhibited synergistically by anti-CD20 and antagonist anti-CD40 antibodies. Therefore the subject-matter of claims 10-18, 25-28, 43-45 and 62-64 involves an inventive step (Article 33(3) PCT).